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Therapeutic Class Review
Dopamine Agonists

Overview/Summary

The two agents included in this class, pramipexole and ropinirole, are nonergot-derivative dopamine agonists that were originally Food and Drug Administration (FDA)-approved for the management of idiopathic Parkinson's disease. Subsequently, the indication for each agent was expanded to include moderate-to-severe primary Restless Legs Syndrome (RLS). The exact mechanism of action of this class of drugs is unknown, but as these conditions appear to be related to dopaminergic dysfunction the benefit of the dopamine agonists may be due to their stimulation of dopamine receptors.[1-6] Both agents are currently involved in ongoing clinical trials in patients with severe or treatment-resistant depression. Pramipexole may also be used off-label for the treatment of fibromyalgia.[7] Parlodel® (bromocriptine) is not discussed in this review and Neupro® (rotigotine transdermal) patch was removed from the market in April of 2008.

These agents have not been compared directly, but they have both demonstrated efficacy in the treatment of both Parkinson's disease and RLS in placebo-controlled trials and with active comparators such as levodopa and bromocriptine in the management of Parkinson's disease. Levodopa has long been the mainstay of therapy for the treatment of Parkinson's disease although its chronic use is associated with the development of dyskinesias. A number of clinical practice guidelines support the use of dopamine agonists for the treatment of early stage Parkinson's disease particularly in younger patients who are more likely to develop the motor complications associated with levodopa. Unfortunately the dopamine agonists are associated with a higher incidence of side effects such as hallucinations, somnolence and edema and are somewhat less effective in managing motor symptoms and deficiencies in activities of daily living than levodopa.[23-27]

The RLS Foundation considers dopamine agonists to be the class of choice in daily RLS, with pramipexole and ropinirole being preferred over ergot-derived dopamine agonists secondary to their more favorable side effect profile.[31] Alternative products used for the treatment of RLS include the anticonvulsants, opioids and benzodiazepines.[2]

Dosing for both pramipexole and ropinirole is recommended three times daily for Parkinson's disease and once daily in the evening for the treatment of RLS. Dosing modifications are recommended with pramipexole in patients with renal impairment. Ropinirole undergoes hepatic metabolism by CYPA12, therefore it has a potential for drug-drug interactions with inducers and inhibitors of this enzyme. Both agents have similar side effect profiles, although pramipexole is more often associated with hallucinations and ropinirole with somnolence and hypertension. Both agents also carry a warning regarding falling asleep during activities of daily living and patients should be advised to avoid potentially dangerous activities including driving.[4-6] Pramipexole is available brand name only as Mirapex®, while ropinirole is available as a branded extended-release formulation (Requip® XL) and as an immediate-release product that is available as brand (Requip®) and generically. Requip® XL does not carry an indication for RLS.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Pramipexole (Mirapex®)	Dopamine agonists	-
Ropinirole (Requip®, Requip® XL)	Dopamine agonists	✔ (immediate release)

XL=extended release.

Indications

Table 2. Food and Drug Administration Approved Indications[4-6]

Indication	Pramipexole	Ropinirole
The treatment of the signs and symptoms of idiopathic Parkinson's disease	✔	✔
The treatment of moderate-to-severe primary Restless Legs Syndrome	✔	✔ (immediate release)

Pramipexole may potentially be used off-label for the treatment of fibromyalgia.[7] Studies evaluating the use of pramipexole and ropinirole in the management of treatment-resistant depression are ongoing.

Pharmacokinetics

Table 3. Pharmacokinetics[4-6]

Generic Name	Bioavailability (%)	Protein Bound (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
Pramipexole	>90	15	Not reported	Renal; 90	None	8-12*
Ropinirole	55	40	Hepatic; CYP1A2	Renal; <10	None	6

*Elderly patients.

Clinical Trials

Numerous clinical trials have compared pramipexole and ropinirole either to placebo or more established medications, such as levodopa, for the management of Parkinson's disease. Studies directly comparing these agents in the treatment of signs and symptoms of idiopathic Parkinson's disease are lacking. A decrease in the risk of developing dyskinesias and other motor complications has been observed with the dopamine agonists compared to levodopa, however levodopa is generally associated with greater improvements in the Unified Parkinson Disease Rating Scale (UPDRS) motor and activities of daily living scores, than pramipexole and ropinirole.[9,11,12] Using neuroimaging, trials have assessed the difference in the rate of progression of dopaminergic degeneration between pramipexole and levodopa treatment (CALM-PD-CIT trial)[9] and between ropinirole and levodopa (REAL-PET study).[12] Results from these trials showed that dopamine agonist therapy is associated with a slower rate of progression compared to levodopa.

Meta-analyses have additionally shown that the dopamine agonists are beneficial as adjunct to levodopa therapy in patients with Parkinson's disease to allow for the reduction in the dose of levodopa, therefore ameliorating the motor complications associated with its long-term use.[14-17]

For the treatment of Restless Legs Syndrome (RLS), the dopamine agonists have each demonstrated greater efficacy over placebo, although head-to-head trials of these agents are not currently available. Pramipexole and ropinirole have each shown benefit in the management of RLS, as demonstrated by improvements in patient and physician assessment scales, as well as sleep and quality of life.[19-22] The results of a meta-analysis evaluating pramipexole, ropinirole, rotigotine and sumanirole in patients with moderate to severe primary RLS as compared to placebo indicated that both pramipexole and ropinirole treatment improved scores on the International RLS Study Group Scale and the Clinical Global Impression-Improvement scale. However, ropinirole showed a significant increase in study withdrawals secondary to adverse events, whereas pramipexole did not.[18] Trials including pramipexole or ropinirole use for the treatment of RLS beyond 12 weeks are lacking.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Parkinson's Disease				
Marek et al[9] Pramipexole 0.5 mg TID increased as needed to maximum of 4.5 mg daily vs carbidopa/levodopa 25/100 mg TID increased as needed to a maximum of 150/600 mg daily Supplemental levodopa was prescribed as needed.	DB, MC, PG, R Patients with early Parkinson's disease requiring dopaminergic therapy	N=82 4 years	Primary: The mean change from baseline in striatal [^{123}I]β-CIT uptake (a useful marker of disease progression) after 46 months Secondary: The percentage and absolute changes from baseline in striatal, putamen, and caudate ^{123}I] β-CIT uptake (a useful marker of disease progression) after 22 and 34 months, clinical severity of Parkinson's disease using the UPDRS 12 hours off medication	Primary: Pramipexole treatment was associated with a slower rate of decline from baseline in striatal [^{123}I]β-CIT uptake with a mean change from baseline of -16.0% (13.3%) compared to -25.5% (14.1%) in the levodopa group (*P*=0.01). Secondary: Pramipexole also demonstrated less of a decline in striatal [^{123}I]β-CIT uptake compared to levodopa at months 22 (-7.1% [9.0] vs -13.5% [9.6]; *P*=0.004) and 34 (-10.9% [11.8] vs -19.6% [12.4]); *P*=0.009). Results were similar for putamen [^{123}I]β-CIT uptake after 22 months (-7.9% [13.7] for pramipexole vs -16.9% [12.9] for levodopa; *P*=0.005) and 34 months (-11.4% [15.3] for pramipexole vs -24.2% [15.5] for levodopa; *P*=0.001), as well as caudate [^{123}I]β-CIT uptake after 22 months (-6.4% [8.8] for pramipexole vs -11.8% [9.4] for levodopa; *P*=0.02) and 34 months (-10.3% [11.7] for pramipexole vs -17.2% [12.4] for levodopa; *P*=0.04). A significant decrease in both the mean total and motor UPDRS scores from baseline was observed in the levodopa group (-3.3 vs 0.9 in the pramipexole group and -2.5 vs 0.0 in the pramipexole group respectively) at month 22. Differences between groups in UPDRS scores did not reach statistical significance at months 34 or 46.
Etminan et al[10] Pramipexole vs ropinirole vs levodopa	MA Patients with Parkinson's disease	N=2,163 (13 trials) Duration not reported	Primary: Adverse events (dizziness, nausea, hypotension, hallucinations, somnolence) Secondary: Not reported	Primary: The pooled RR of pramipexole and ropinirole compared to levodopa was reported and it was determined that the dopamine agonists were associated with a significantly greater risk of somnolence (RR, 1.61; 95% CI, 1.21 to 2.13) and hallucinations (RR, 1.92; 95% CI, 1.08 to 3.24) than levodopa, however the difference in the risk of developing dizziness (RR, 0.96; 95% CI, 0.61 to 1.51), hypotension (RR, 1.01; 95% CI, 0.67 to 1.51) and nausea (RR, 1.13; 95% CI, 0.92 to 1.39) did not reach statistical significance. The pooled data of the comparison between the dopamine agonists to placebo showed a significantly increased risk with active treatment of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				dizziness (RR, 1.60; 95% CI, 1.17 to 2.20), hypotension (RR, 2.14; 95% CI, 1.02 to 4.48), nausea (RR, 2.15; 95% CI, 1.16 to 2.75), somnolence (RR, 3.16; 95% CI, 1.62 to 6.13) and hallucinations (RR, 4.24; 95% CI, 1.87 to 9.62). There was a significantly higher risk of developing hypotension associated with ropinirole use (RR, 6.46; 95% CI, 1.47 to 28.28) than with pramipexole use (RR, 1.65; 95% CI, 0.88 to 3.08) compared to placebo, but not when the individual agents were compared to levodopa (RR, 1.03; 95% CI, 0.62 to 1.63 for ropinirole compared to RR, 1.12; 95% CI, 0.30 to 4.19 for pramipexole). The RR of somnolence reported with ropinirole was 5.73 (95% CI, 2.34 to 14.01) compared to 2.01 (95% CI, 2.17 to 3.16) for pramipexole relative to placebo although a significant difference was not demonstrated in comparison to levodopa. Pramipexole was associated with a higher risk of hallucinations than ropinirole compared to placebo (RR, 5.20; 95% CI, 1.97 to 13.72 compared to RR, 2.75; 95% CI, 0.55 to 13.73), but not when compared with levodopa. Secondary: Not reported
Inzelberg et al[11] Pramipexole vs ropinirole vs cabergoline vs	SR Patients with early Parkinson's disease	N=981 (3 trials) 2-5 years	Primary: Proportion of patients who developed dyskinesia, patient withdrawals, change from baseline in scores for motor function and activities of daily living, adverse events Secondary: Not reported	Primary: Fewer patients developed dyskinesia with dopamine agonist use than with levodopa treatment (P<0.01 for all three). The decrease in risk was similar among groups with an OR of 0.25 (95% CI, 0.13 to 0.47) for pramipexole, 0.31 (95% CI, 0.18 to 0.53) for ropinirole and 0.38 (95% CI, 0.19 to 0.78) for cabergoline all compared to levodopa. Differences in the incidence of withdrawals relative to levodopa did not reach statistical significance for ropinirole (OR, 1.13; 95% CI, 0.68 to 1.88), pramipexole (OR, 1.24; 95% CI, 0.64 to 2.39) or cabergoline (OR, 1.24; 95% CI, 0.71 to 2.14). Improvements in motor function were found to be greater in the levodopa treatment arm than both pramipexole (P=0.001) and ropinirole (P=0.008).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
levodopa				The adjusted mean changes in the motor scores were reported as 3.90 for pramipexole and 4.48 for ropinirole with a difference of 0.58 (95% CI, -4.20 to 3.13; *P*=0.759), thus the difference between each dopamine agonist compared to levodopa was comparable. Levodopa also demonstrated a significantly greater benefit in ADL's over pramipexole (*P*<0.001), but not ropinirole (*P*=0.08). The adjusted mean changes in the ADL scores were reported as 5.000 for pramipexole and 1.530 for ropinirole with a difference of 3.470 (95% CI, 0.363 to 6.580; *P*=0.029). Results of these two outcomes were not reported for cabergoline. The incidence of edema was reported more often in the dopamine agonist arms as opposed levodopa. Odds ratios were reported as 4.09 (95% CI, 1.61 to 10.41) for pramipexole, 2.73 (95% CI, 1.01 to 7.39) for ropinirole and 6.22 (95% CI, 2.55 to 15.21) for cabergoline. There were no significant differences in the absolute risk reduction. The frequency of other adverse events including anxiety, depression, headache, dizziness/hypotension and nausea did not differ significantly among each of the dopamine agonists or compared to levodopa (*P*>0.1). Somnolence was only reported in trials comparing pramipexole or ropinirole to levodopa and occurred more often with pramipexole (*P*=0.032 vs levodopa) but not with ropinirole relative to levodopa (*P*=0.175). Secondary: Not reported
Whone et al[12] Ropinirole 0.25 mg TID increased to a maxium of 24 mg/day as needed vs carbidopa/levodopa	DB, MC, PRO, R Patients 30 to 75 years of age with ^{18}F-dopa PET evidence and a clinical diagnosis of Parkinson's	N=162 2 years	Primary: Change in putamen ^{18}F-dopa uptake (Ki) (a useful marker of disease progression) from baseline Secondary: Change from baseline in USDRS motor	Primary: A significantly greater reduction in putamen Ki was observed with levodopa treatment (-20.30% [SE, 2.35]) relative to ropinirole therapy (-13.40% [SE, 2.14]); 95% CI, 0.65 to 13.06; *P*=0.022). Secondary: Ropinirole therapy was associated with an increase in the UPDRS motor score (0.70 points; SE, 0.97), while levodopa demonstrated a reduction in the score (-5.64 points; SE, 1.05) and therefore an improvement in symptoms. The difference in the change in motor function between levodopa and

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12.5/50 mg aily increased to a maximum of 1,000 mg of levodopa as needed Supplemental levodopa was prescribed as needed. Fixed dose amantadine and anticholinergic antiparkinson medications were permitted.	disease, experiencing symptoms for ≤2 years		scores, proportion of patients scoring 1 (very much improved) or 2 (much improved) on the CGI global improvement scale over 1 year, incidence and time to development of dyskinesias	ropinirole was significant (95% CI, 3.54 to 9.14). The percentage of patients reporting either a 1 or a 2 on the CGI global improvement scale was comparable between groups (67.80% for ropinirole vs 74.70% for levodopa; OR, 0.72; 95% CI, 0.36 to 1.45; *P*=0.367). There was a significant reduction in the risk of developing dyskinesias with ropinirole (3.40%) relative to levodopa (26.70%; OR, 0.09; 95% CI, 0.02 to 0.29; *P*<0.001). The difference in time to development of dyskinesias was significant and also favored ropinirole (*P*<0.001). Supplemental levodopa was required in 15 (17.0%) patients in the ropinirole group and 7 (9.0%) in the levodopa group. The most common adverse drug reactions noted were nausea and somnolence and both were more often associated with ropinirole use (43.7% and 37.9% respectively vs 21.3% and 9.3% for levodopa).
Stowe et al[13] Dopamine agonists with or without levodopa vs levodopa or dopamine agonists with or without levodopa vs placebo or	MA Patients of any age with early idiopathic Parkinson's disease, no history of motor complications, either untreated or with limited exposure to anti-parkinsonian medications	N=5,247 (29 trials) 8 weeks – 10 years	Primary: Symptom control, motor complications, side effects, withdrawals Secondary: Not reported	Primary: Levodopa was reported to be of benefit over dopamine agonists in overall symptom control, although there was insufficient data available to meta-analyze results. Freezing was noted more often with dopamine agonist therapy relative to levodopa (OR, 1.58; 95% CI, 1.14 to 2.18; *P*=0.005), but this outcome was only reported in 5 trials. Compared to placebo, dopamine agonist therapy was associated with significant improvements in symptom control. The risk of developing motor complications was reduced in patients receiving agonist therapy compared to levodopa, including dyskinesia (OR, 0.51; 95% CI, 0.43 to 0.59; *P*<0.00001), dystonia (OR, 0.64; 95% CI, 0.51 to 0.81; *P*=0.0002) and motor fluctuations (OR, 0.75; 95% CI, 0.63 to 0.90; *P*=0.002). Conversely, there was an increased risk of developing non-motor side effects associated with dopamine agonist use vs levodopa. Edema (OR, 3.68; 95% CI, 2.62 to 5.18; *P*<0.00001), somnolence (OR, 1.49;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dopamine agonists with or without levodopa vs levodopa and placebo				95% CI, 1.12 to 2.00; *P*=0.007), constipation (OR, 1.59; 95% CI, 1.11 to 2.28; *P*=0.01), dizziness (OR, 1.45; 95% CI, 1.09 to 1.92; *P*=0.01), hallucinations (OR, 1.69; 95% CI, 1.13 to 2.52; *P*=0.01) and nausea (OR, 1.32; 95% CI, 1.05 to 1.66; *P*=0.02) were all more frequently reported in patients taking dopamine agonists than with levodopa. Subsequently, a greater number of patient in the dopamine agonist group discontinued treatment secondary to side effects (OR, 2.49; 95% CI, 2.08 to 2.98; *P*<0.00001). Analysis between individual agonists was reported in regards to reduction in dyskinesia. There was a 59% decrease in dyskinesia for both cabergoline and pergolide, 71% for both pramipexole and ropinirole and 35% decrease with bromocriptine (*P*=0.008). Secondary: Not reported
Clarke et al[14] Pramipexole vs placebo	MA Patients with a clinical diagnosis of idiopathic Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose deterioration	N=669 (4 trials) >4 weeks	Primary: Off time measurements, changes in dyskinesia rating scale and the prevalence of dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy and/or adverse events Secondary: Not reported	Primary: Pramipexole resulted in a greater reduction in off time compared to placebo with weighted mean difference of 1.8 hours (95% CI, 1.2 to 2.3; *P*=0.00001). The incidence of dyskinesia was more frequent in the pramipexole treatment group compared to placebo (OR, 2.10; 95% CI, 1.50 to 2.94; *P*=0.00002 vs placebo). A significant improvement in UPDRS complication score was noted in 2 of the 4 trials, in UPDRS ADL scores in all trials and in UPDRS motor scores in 3 trials. Pramipexole showed a significant benefit in the reduction in the dose of levodopa (weighted mean difference of 115 mg; 95% CI, 87 to 143; *P*<0.00001) and a significantly lower withdrawal rate (OR, 0.64; 95% CI, 0.44 to 0.93; *P*=0.02). Secondary: Not reported
Clarke et al[15] Pramipexole	MA Patients with a clinical	N=163 (1 trial) >4 weeks	Primary: Off time measurements, changes in dyskinesia	Primary: Pramipexole therapy resulted in a greater reduction in off time compared to bromocriptine with weighted mean difference of 1.4 hours (95% CI, 0.03 to 2.77; *P*=0.05).

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vs bromocriptine	diagnosis of idiopathic Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose deterioration		rating scale and the prevalence of dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy and/or adverse events Secondary: Not reported	The differences in the prevalence of dyskinesia, changes in the dyskinesia rating scale, or UPDRS complication score was not significant. Improvements in the UPDRS ADL and motor scores, as well as the levodopa dose reduction were comparable with both agents. There was no significant difference in the withdrawal rate. Secondary: Not reported
Clarke et al[16] Ropinirole vs placebo	MA Patients with a clinical diagnosis of idiopathic Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose deterioration	N=263 (3 trials) >4 weeks	Primary: Off time measurements, changes in dyskinesia rating scale and the prevalence of dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy and/or adverse events Secondary: Not reported	Primary: There was inadequate data available to determine the effect of ropinirole on off time. The incidence of dyskinesia was significantly more frequent with active treatment (OR, 2.90; 95% CI, 1.36 to 6.19). Ropinirole demonstrated a significant benefit in the reduction in the dose of levodopa (weighted mean difference of 180 mg; 95% CI, 106 to 253). There was no significant difference in the withdrawal rate reported (OR, 0.52; 95% CI, 0.24 to 1.09). A significant difference in the number of patients considered to be much/very much improved was found and favored ropinirole (OR, 2.98; 95% CI, 1.53 to 5.80; *P*=0.001). Secondary: Not reported
Clarke et al[17] Ropinirole vs	MA Patients with a clinical diagnosis of	N=482 (3 trials) >4 weeks	Primary: Off time measurements, changes in the prevalence of	Primary: No significant difference was established between comparators in off time (weighted mean difference, 0.80; 95% CI, -0.80 to 1.69), prevalence of dyskinesia (OR, 1.51; 95% CI, 0.65 to 3.49), patients reporting much/very much improved on the CGI (OR,1.36; 95% CI, 0.87 to 2.13), levodopa dose

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bromocriptine	idiopathic Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose deterioration		dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy and/or adverse events Secondary: Not reported	reduction (weighted mean difference, 50.21; 95% CI, -49.40 to 149.81) or withdrawal rates (OR, 0.76; 95% CI, 0.45 to 1.27). Secondary: Not reported
Restless Legs Syndrome				
Baker et al[18] Pramipexole 0.125 to 0.750 mg/day vs ropinirole 0.25 to 6.00 mg/day vs rotigotine 0.5 to 4.5 mg/day vs sumanirole 0.5 to 4 mg/day	MA Patients with a mean age of 51 to 76 years old with moderate-to-severe RLS	N=3,197 (14 trials) 1-12 weeks	Primary: Percentage of responders to medications determined by the CGI-I scale, adjusted mean change in the IRLS score (10 endpoints ranging from 4=very severe to 0=none, maximum score of 40) from baseline Secondary: Safety	Primary: As a class, the nonergot dopamine agonists demonstrated a significantly greater response as measured by the CGI-I scale compared to placebo (RR, 1.36; 95% CI, 1.24 to 1.49). Upon subgroup analysis, each individual agent, with the exception of sumanirole, also showed a significantly greater effect for pramipexole (RR, 1.60; 95% CI, 1.34 to 1.92) vs ropinirole (RR, 1.32; 95% CI, 1.21 to 1.43) vs rotigotine (RR, 1.41; 95% CI, 1.12 to 1.79) vs sumanirole (RR, 0.96; 95% CI, 0.71 to 1.30). Results of the second outcome significantly favored nonergot dopamine agonist treatment with a weighted mean difference in the IRLS score of -4.83 (95% CI, -6.42 to -3.43) for the class, -7.16 (95% CI, -9.77 to -4.54) for pramipexole and -3.50 (95% CI, -4.75 to -2.25) for ropinirole. Results were not reported for rotigotine or sumanirole. Secondary: An increased risk of withdrawal was observed as a class relative to placebo (RR, 1.35; 95% CI, 1.00 to 1.81), however only ropinirole was associated with a significant difference in withdrawal upon subgroup analysis (RR, 1.49; 95% CI, 1.06 to 2.10) compared to pramipexole (RR, 1.15; 95% CI, 0.49 to 2.69), rotigotine (RR, 0.46; 95% CI, 0.08 to 2.58) and sumanirole (RR, 1.11; 95% CI, 0.06 to 19.45).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oertel et al[19] Pramipexole 0.125 mg daily, dose could be increased in weekly intervals to a maximum of 0.750 mg daily vs placebo	DB, MC, RCT Male and female patients between 18 and 80 years of age with a diagnosis of primary RLS and moderate to severe symptoms (baseline score of >15 on the IRLS) present for at least 2-3 days weekly	N=345 6 weeks	Primary: Change from baseline in the IRLS ranging from 0 (none) to 4 (very severe), CGI-I responders (proportion of patients with CGI-I assessments of "much/very much improved") Secondary: Proportion of PGI responders (patients reporting their condition as "much/very much better"), IRLS responders (reduction from baseline in IRLS score of ≥50%), severity of RLS symptoms on a scale of 0 (not present) to 100 (severe) using a VAS, safety	Primary: Improvements from baseline in the IRLS score was significantly greater in the pramipexole treatment group compared to placebo (-12.3; SE, ±0.6 vs -5.7; SE, ±0.9; difference of -6.6; SE, ±1.1; 95% CI, -8.6 to -4.5; *P*<0.001). More patients in the active treatment group (62.9%) were considered to be CGI-I responders than placebo (32.5%; *P*<0.0001). Secondary: A greater proportion of patients were determined to be both IRLS and PGI responders in the pramipexole treatment group vs placebo (52.5% vs 28.9% and 61.6% vs 31.6% respectively; *P*< 0.0001 for both outcome measures). Pramipexole demonstrated benefit over placebo in severity of symptoms while getting to sleep (-30.6; SE, ±1.9 vs -13.8; SE, ±2.7; *P*<0.0001), during the course of the night (-32.3; SE, ±2.0 vs -12.4; SE ±2.7; *P*<0.0001) and during the day (-12.1; SE, ±1.5 vs -1.5; SE, ±2.1; *P*<0.0001). The most frequently reported side effects associated with active treatment included nausea (9.6% vs 5.2% with placebo), fatigue (9.1% vs 4.3% with placebo) and headache (7.0% vs 6.1% with placebo).
Winkelman et al[20] Pramipexole 0.25 mg daily vs pramipexole 0.50 mg daily	DB, PC, RCT Men and women between the ages of 18 and 80 with moderate to severe RLS (baseline score	N=344 12 weeks	Primary: Patient ratings of symptoms severity on the IRLS, CGI-I responder rate Secondary: IRLS responder rate, patient global	Primary: Each active treatment group demonstrated a significantly greater improvement in IRLS scores from baseline compared to placebo (-12.8 for 0.25 mg, -13.8 for 0.50 mg, -14.0 for 0.75 mg vs -9.3 for placebo; all *P*<0.01). Seventy-two percent of patients treated with pramipexole were designated responders vs 51.2% of placebo (*P*=0.0005). Individual results were also significant and were reported as 74.7% for the 0.25 mg dose (*P*<0.0005), 67.9% for the 0.50 mg dose (*P*<0.0484) and 72.9% for the 0.75 mg dose

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pramipexole 0.75 mg daily vs placebo	of ≥15 on the IRLS) at least 2-3 days weekly		impression measured by PGI, symptom severity per VAS ratings on a scale from 0 (not present) to 100 (severe), daytime somnolence measured by ESS, quality of life measured by Johns Hopkins RLS-QOL	(*P*<0.0038). Secondary: The IRLS responder rate was significantly greater with active treatment (61.4% - 62.1%) over placebo (42.4%; *P*<0.05 for all groups vs placebo). Results were similar for PGI responder rate as well, with 61.4% of pramipexole patients and 44.7% of those on placebo meeting criteria (*P*=0.0056). However, when assessed individually, only the difference between the 0.25 mg group and placebo group reached statistical significance (*P* value not reported). Changes from baseline in RLS symptom severity while getting to sleep (-43.1 vs -29.0; *P*=0.0001), during the night (-41.3 vs -24.3; *P*<0.0001), during the day (-16.0 vs -9.2; *P*=0.0081), as well as satisfaction with sleep (-38.4 vs -25.8; *P*=0.0016) all significantly favored pramipexole treatment over placebo, yet the difference in daytime somnolence between active therapy and placebo did not reach statistical significance (*P*=0.3028). Individual dose results were not reported. Greater improvements in quality of life scores were evident with pramipexole compared to placebo at all doses (19.2±1.4; *P*=0.0041 for 0.25 mg, 21.3±1.5; *P*=0.0002 for 0.50 mg, 19.5±1.4; *P*=0.0029 for 0.75 mg and 13.5±1.4 for placebo).
Trenkwalder et al[21] Ropinirole 0.25 to 4.00 mg daily vs placebo	DB, PC, MC, RCT Men and women between the ages of 18 and 79 diagnosed with RLS and a baseline score of >15 on the IRLS and experiencing symptoms at	N=284 12 weeks	Primary: Mean change from baseline in the total IRLS score to week 12 Secondary: Proportion of patients with CGI-I assessments of "much/very much improved", mean change from baseline in the total IRLS score	Primary: Improvements from baseline to week 12, in the mean total IRLS score, was significantly greater in the ropinirole treatment group compared to placebo (-11.04 vs -8.03; adjusted difference of -3.01; 95% CI, -5.03 to -0.99; *P*=0.0036). Secondary: A significantly greater proportion of patients met CGI-I criteria in the active arm compared to placebo (53.4% vs 40.9%; OR, 1.7; 95% CI, 1.02 to 2.69; *P*=0.0416). Improvements from baseline to the first week of treatment, in the mean total IRLS score, was significantly greater with ropinirole compared to placebo (-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	least 15 nights/month in the previous month or prior to treatment		to week 1, impact of treatment on sleep, quality of life using the RLS QOL questionnaire, safety	8.19 vs -5.14; adjusted difference of -3.05; 95% CI, -4.72 to -1.38; *P*=0.0004). Significant improvements in sleep adequacy (*P*=0.0015), quantity (*P*=0.0331), daytime somnolence (*P*=0.0064) and sleep disturbance (*P*=0.0245) was observed with ropinirole treatment relative to placebo. Similarly, significant improvement in quality of life scores was shown with active treatment compared to placebo (17.1 for ropinirole vs 12.6 for placebo; *P*=0.0314). Nausea and headache were the most commonly reported side effects and both occurred more often in the ropinirole treatment arm (37.7% and 19.9%, respectively for ropinirole vs 6.5% and 16.7% for placebo).
Walters et al[22] Ropinirole 0.125 to 4 mg daily vs placebo	DB, MC, RCT Men and women between the ages of 18 and 79 with a diagnosis of primary RLS and a baseline score of ≥15 on the IRLS and experiencing symptoms at least 15 nights/month in the previous month or prior to treatment	N=267 12 weeks	Primary: Change in IRLS score at week 12 Secondary: Proportion of patients with CGI-I assessments of "much/very much improved" at week 12 and week 1, time to response on the CGI-I scale, change in IRLS scale score at week 1, time to response (reduction of 6 points) on the IRLS, change from baseline in domains of the MOS sleep scale, the RLS QOL questionnaire, the MOS SF-36 Health Survey and the WPAI questionnaire	Primary: Improvements from baseline to week 12, in the mean total IRLS score, was significantly greater in the ropinirole treatment group compared to placebo (-11.2 [SE, 0.76] vs -8.7 [SE, 0.75]; adjusted difference of -2.5; 95% CI, -4.6 to -0.4; *P*=0.0197). Secondary: A significantly greater proportion of patients met CGI-I criteria in the active arm compared to placebo at week 12 (59.5% vs 39.6%; OR, 2.3; 95% CI, 1.4 to 3.8; *P*=0.001). Similar results were found in regards to CGI-I scores at week 1, with 36.6% of patients on ropinirole and 16.4% of placebo patients considered as responders (OR, 3.0 (95% CI, 1.7 to 5.3; *P*=0.0003). The median time to a response also favored ropinirole (14 days) over placebo (22 days; *P*=0.0004). Improvements in the IRLS score from baseline to the first week of treatment was significantly greater with ropinirole compared to placebo (-8.4 [SE, 0.62] vs -4.8 [SE, 0.62]; adjusted difference of -3.5; 95% CI, -5.3 to -1.8; *P*<0.0001), although the difference in median time to a response did not reach statistical significance (*P*=0.0588). Ropinirole treatment was associated with significant improvements in daytime somnolence (adjusted treatment difference, -6.3; 95% CI, -10.0 to -2.0; *P*=0.0043), sleep disturbance (adjusted treatment difference, -13.4; 95% CI, -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				18.8 to -8.1; *P*<0.0001), sleep adequacy (13.6; 95% CI, 7.2 to 20.0; *P*<0.0001) and sleep quantity (adjusted treatment difference, 1.3 hours; 95% CI, 0.3 to 2.2; *P*=0.0097). Other endpoints that achieved a statistically significant difference, all of which favored ropinirole over placebo, included the overall life-impact score on the RLS QOL questionnaire (17.40 [SE, 1.42] vs 12.90 [SE, 1.40];adjusted treatment difference, 4.4; 95% CI, 0.5 to 8.4; *P*=0.0263), as well as the mental-health domain (adjusted treatment difference, 5.2; 95% CI, 1.7 to 8.7; *P*=0.0041), social functioning (adjusted treatment difference, 5.7; 95% CI, 0.5 to 10.9; *P*=0.0331) and vitality (adjusted treatment difference, 6.3; 95% CI, 1.9 to 10.6; *P*=0.0049) on the SF-36 Health Survey. Differences in the WPAI questionnaire scores did not achieve statistical significance. Nausea and fatigue were the most frequently reported side effects and were observed more often in the ropinirole group (39.7% and 15.3% respectively for ropinirole vs 8.1% and 6.6% for placebo). Headache was also commonly reported but occurred more often in the placebo group (25.7% vs 22.1% of ropinirole).

Drug regimen abbreviations: TID=three times daily
Study abbreviations: DB=double-blind, CI=confidence interval, MA=meta-analysis, MC=multicenter, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RR=relative risk, SE=standard error, SR=systematic review
Miscellaneous abbreviations: ADL=activities of daily living, CGI=Clinical Global Impression, CGI-I=Clinical Global Impressions-improvement, ESS=Epworth Sleepiness Scale, IRLS=International RLS Study Group Rating Scale, MOS=Medical Outcomes Study, PET=positron emission tomography, PGI=Patient Global Impression, QOL=quality of life, RLS=restless legs syndrome, SF=Short Form, UPDRS=Unified Parkinson Disease Rating Scale, VAS=Visual Analogue Scale, WPAI=work productivity and activity impairment

Special Populations

Table 5. Special Populations[4-6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Pramipexole	No dosage adjustment required in elderly. Safety and efficacy not established in children.	Dose adjustment required in patients with mild to severe renal impairment. Not adequately studied in patients with a creatinine clearance < 15 mL/min and hemodialysis patients.	Not studied in hepatic dysfunction.	C	Unknown
Ropinirole	No dosage adjustment required in elderly. Safety and efficacy not established in children.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown

Adverse Drug Events

The following table presents the most common (≥5%) adverse events reported with the dopamine agonists. The adverse events that were reported most frequently in patients with either Parkinson's disease or restless leg syndrome were nausea, dizziness and somnolence. Motor complications associated with these agents, such as dyskinesia, were reported in clinical trials involving patients with advanced Parkinson's disease generally on adjunctive levodopa therapy. Cognitive symptoms such as hallucinations occurred with increased frequency in patients over the age of 65.

Table 6. Adverse Drug Events (%)[4-6]

Adverse Event	Pramipexole	Ropinirole
Cardiovascular		
Hypertension	-	5
Orthostatic symptoms	-	6
Peripheral edema	2-5	2-7
Postural hypotension	53*	-
Syncope	-	3-12
***Central Nervous System**		
Amnesia	4-6	5*
Confusion	4-10	5-9
Dizziness	25-26	11-40
Dream abnormalities	11*	-
Dry Mouth	3-7	3-5
Dyskinesia	47*	34*
Dystonia	2-8	-
Extrapyramidal syndrome	28*	-
Fatigue	3-9	8-11
Gait abnormalities	7*	-

Adverse Event	Pramipexole	Ropinirole
Hallucinations	9-17	5-10
Headache	16	17
Hypertonia	7*	-
Hypokinesia	-	5
Insomnia	9-27	-
Paresthesia	-	3-5
Somnolence	6-22	12-40
Tremor	-	6*
Increased sweating	-	3-7
Gastrointestinal		
Abdominal pain/discomfort	-	3-9
Constipation	4-14	6
Diarrhea	1-7	5
Dyspepsia	-	4-10
Nausea	11-28	30-60
Vomiting	-	7-12
Musculoskeletal		
Arthralgia	-	4-7
Asthenia	10-14	6
Other		
Abnormal vision	-	6
Accidental injury	17*	-
Anxiety	-	6
Falls	-	10*
General edema	4-5	6
Increased drug level	-	7
Nasal congestion	3-6	-
Nervousness	-	5
Pain	3-7	5-8
Pharyngitis	-	6-9
Urinary Frequency	6*	-
Viral Infection	-	11
Upper respiratory tract infection	-	6
Urinary tract infection	-	5-6

- Event not reported or incidence <5%.
*Reported in clinical trials in patients with advanced Parkinson's disease possibly receiving concomitant levodopa therapy.

Contraindications[4-6]
Pramipexole and ropinirole are contraindicated in patients with a known hypersensitivity to the respective product.

Warnings/Precautions[4-6,8]
The dopamine agonists carry several warnings including falling asleep during activities of daily living, symptomatic hypotension and hallucinations.

Patients treated with pramipexole and ropinirole have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on pramipexole and ropinirole, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as 1 year after the initiation of treatment.

Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, patients should be continually reassessed for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Also patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with pramipexole, patients should be advised of the potential to develop drowsiness and should be specifically asked about factors that may increase the risk with pramipexole such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (eg, cimetidine). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (eg, conversations, eating), pramipexole discontinuation should be considered. If a decision is made to continue pramipexole, patients should be advised not to drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living

Somnolence is a common occurrence in patients receiving pramipexole at doses above 1.5 mg/day (0.5 mg 3 times per day). In controlled clinical trials in restless leg syndrome patients treated with pramipexole tablets at doses of 0.25 to 0.75 mg once daily, the incidence of somnolence was 6% compared with an incidence of 3% for placebo-treated patients. In controlled clinical trials, somnolence was a common occurrence in patients receiving ropinirole and was more frequent in Parkinson disease (up to 40% ropinirole, 6% placebo) than in restless leg syndrome (12% ropinirole, 6% placebo).

Dopamine agonist use has been associated with orthostatic/postural hypotension therefore, patients should be observed for signs and symptoms of the condition particularly upon initiating therapy or with any increase in dose. Hallucinations have been reported with both agents with increased incidence in the elderly population.

Abrupt withdrawal or dose reduction in antiparkinson therapy has been associated with symptoms similar to neuroleptic malignant syndrome, although this effect has not specifically been linked to pramipexole or ropinirole use. Fibrotic complications, such as retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion and pericarditis have been related to ergot-derived dopamine agonists; however the risk with pramipexole or ropinirole use is also unknown. Rebound, or the change of restless leg syndrome symptoms to early morning, and augmentation (an escalation in overall symptoms, symptoms occurring in the early evening/afternoon or symptoms effecting areas other than the legs) have been reported with dopaminergic medications but have not been demonstrated during clinical trials with pramipexole or ropinirole. Compulsive behaviors have also been observed in individuals treated with dopaminergic agents for Parkinson's disease.

Drug Interactions[4-6]

There are no significant drug interactions listed for pramipexole. Ropinirole is metabolized by the enzyme CYP1A2, therefore there is the potential for an alteration in clearance of this agent with inhibitors (i.e. ciprofloxacin, fluvoxamine) and inducers (i.e. omeprazole, cigarette smoking) of CYP1A2.

Dosage and Administration

Table 7. Dosing and Administration[4-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Pramipexole	Parkinson's disease: Initial: 0.375 mg/day given in three divided doses and should not be increased more frequently than every 5 to 7 days; maintenance, 1.5 to 4.5 mg/day	Safety and efficacy in pediatrics have not	Tablet: 0.125 mg 0.25 mg 0.5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	administered in equally divided doses three times per day Renal Impairment: normal to mild impairment (creatinine Cl>60 mL/min) initial: 0.125 mg 3 times daily; maximum, 1.5 mg 3 times daily; moderate impairment (creatinine Cl=35 to 59 mL/min) initial: 0.125 mg twice daily; maximum, 1.5 mg twice daily; severe impairment (creatinine Cl=15 to 34 mL/min) initial: 0.125 mg once daily; maximum, 1.5 mg once daily; very severe impairment (creatinine Cl<15 mL/min and hemodialysis patients): pramipexole has not been adequately studied in this group of patients Restless legs syndrome: Initial: 0.125 mg taken once daily 2-3 hours before bedtime; for patients requiring additional symptomatic relief, the dose may be increased every 4 to 7 days to 0.5 mg once daily Renal impairment: severe and moderate renal impairment (creatinine Cl=20-60 mL/min): duration between titration steps should be increased to 14 days	been established.	0.75 mg 1 mg 1.5 mg
Ropinirole	Parkinson's disease: Immediate-release tablet: Initial: 0.25 mg three times daily, based on individual patient response, dosage should then be titrated with weekly increments; after week 4, if necessary, daily dosage may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by up to 3 mg/day weekly to a total dose of 24 mg/day Sustained-release tablet: Initial: 2 mg taken once daily for 1 to 2 weeks followed by increases of 2 mg/day at weekly or longer intervals as appropriate, depending on therapeutic response and tolerability, up to a maximally recommended dose of 24 mg/day Restless Legs Syndrome: Immediate-release tablet: Initial: 0.25 mg once daily, 1 to 3 hours before bedtime, after 2 days, the dosage can be increased to 0.5 mg once daily and to 1 mg once daily at the end of the first week of dosing, then increased in increments of 0.5 mg weekly to a maximum total dose of 4 mg once daily	Safety and efficacy in pediatrics have not been established.	Extended-release tablet: 2 mg 4 mg 8 mg 12 mg Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg 5 mg

Cl=clearance.

Clinical Guidelines

According to the National Institute for Health and Clinical Excellence (NICE) there is no universal first-choice therapy for patients with Parkinson's disease.[25] Levodopa, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors may all be used in patients with early Parkinson's disease for symptomatic treatment. The MAO-B inhibitors are considered more convenient compared to the other agents due to ease of administration and may be considered in patients who need symptomatic treatment prior to the administration of dopaminergic therapy. Anticholinergics should be limited to younger patients with early Parkinson's disease associated with severe tremor. In elderly patients, early use of levodopa is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events.

In addition, there is no single agent of choice for late stage Parkinson's disease.[25] Levodopa, dopamine agonists, MAO-B inhibitors and catechol-O-methyl transferase (COMT) inhibitors may all be considered to reduce motor fluctuations in patients with late stage Parkinson's disease. For the symptomatic control of wearing-off in late, complicated Parkinson's disease, several strategies have been recommended. Such strategies include increasing the dosing frequency of levodopa or switching to a controlled-release formulation of the medication. Also adding a COMT-inhibitor, MAO-B inhibitor or dopamine agonist as adjunctive therapy is also recommended. If these strategies fail it is recommended that amantadine or an anticholinergic be considered. For the symptomatic control of dyskinesias in late, complicated Parkinson's disease the addition of amantadine is recommended. Other strategies include reducing the dose size of levodopa or discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors, however these strategies increase the risk of worsening off-time.

Table 8. Clinical Guidelines

Clinical Guideline	Recommendation(s)
National Institute for Health and Clinical Excellence (NICE): **Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care (2006)**[25]	• There is no universal first-choice therapy for patients with Parkinson disease (PD). Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early PD for symptomatic treatment with doses kept as low as possible to reduce the development of motor complications. • Dopamine agonists may be used in patients with early PD for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if the patient fails therapy or side effects prevents titration. • Monoamine oxidase-B (MAO-B) inhibitors may be used in patients with early PD for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early PD, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early PD for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric side effects. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early PD. • Most patients with PD will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage PD. • There is no single agent of choice for late stage PD. • Extended-release levodopa may help reduce motor complications in patients with late stage PD, but is not considered a first-line agent.

Clinical Guideline	Recommendation(s)
	• Dopamine agonists may be used to reduce motor fluctuations in patients with late stage PD. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if side effects prevent titration. • MAO-B inhibitors may be used to reduce motor fluctuations in patients with late stage PD. • Catechol-O-methyl transferase (COMT) inhibitors may be used to reduce motor fluctuations in patients with late stage PD. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage PD. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.
American Academy of Neurology (AAN) Practice Parameter: **Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)**[23]	• Patients with PD, who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in PD, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living (ADL) in patients with PD who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor complications and ADL disability and is associated with a higher incidence of dyskinesias than dopamine agonists. • Levodopa or a dopamine agonist may be initiated in patients with PD who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (i.e., wearing off, dyskinesias, on-off fluctuations) compared to levodopa. • Treatment with a dopamine agonist was associated with more frequent adverse drug reactions (hallucinations, somnolence and edema in the lower extremities) than levodopa. • When initiating treatment with levodopa in patients with PD, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
AAN Practice Parameter: **Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)**[24]	• Rasagiline and entacapone demonstrated statistically significant reduction in off time as compared to placebo in clinical trials. It is recommended that these two agents should be offered to reduce off-time. • Pergolide demonstrated some improvement in the reduction in off-time as compared to placebo in clinical trials. However, a large number of patients on pergolide experienced more dyskinesias. Pramipexole demonstrated some reduction in off-time in placebo controlled trials. Ropinirole and tolcapone showed reduction in off-time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce off-time. Due to side effects and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing off-time. It is recommended that these agents may be considered to reduce off-time. • Bromocriptine and extended-release carbidopa/levodopa do not help to

Clinical Guideline	Recommendation(s)
	reduce off-time. • Amantadine demonstrated reduction in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with PD for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in PD patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Early (Uncomplicated) Parkinson's Disease (2006)**[26]	• No adequate clinical trials have been conducted to provide definitive evidence for pharmacological neuroprotection. • In the management of early PD, MAO-B inhibitors have a modest benefit in treating the symptomatic complications of PD compared to levodopa and dopamine agonists. These agents are more convenient due to the ease of administration (i.e., one dose, once daily, no titration). • Amantadine and anticholinergics offer minimal symptom control compared to levodopa. • Anticholinergics are poorly tolerated in the elderly and use should be restricted to younger patients. • Levodopa is the most effective anti-Parkinson's drug for symptomatic relief. • Early use of levodopa in the elderly is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events. • Pramipexole and ropinirole are effective dopamine agonists as monotherapy in the treatment of early stage PD. • Convincing evidence that older agents in the class are less effective than the newer non-ergot agents is lacking. • Dopamine agonists have a lower risk of developing motor complications than compared to levodopa. These agents do have a greater incidence of adverse effects which include hallucinations, somnolence and edema in the lower extremities. • Younger patients should be started on a dopamine agonist as initial treatment to prolong the use of levodopa and the development of motor complications.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Late (Complicated) Parkinson's Disease (2006)**[27]	<u>Symptomatic Control of Wearing-off</u> • Adjusting the levodopa dose by increasing the dosing frequency has been beneficial to control off-time. • Switching from the standard formulation of levodopa to the controlled-release formulation improves wearing-off symptoms. • Adding a COMT-inhibitor or a MAO-B inhibitor is effective in reducing off-time by 1-1.5 hours/day. • Adding a dopamine agonist provides modest benefit. All dopamine agonists are equally effective and efficacious in reducing off-time. Pergolide and other ergot derivatives are reserved for second-line use, due to the adverse effect of valvulopathy. • Addition of amantadine or anticholinergics should be considered in patients with severe off symptoms who fail the recommended strategies listed above. <u>Symptomatic Control of Dyskinesias</u> • Patients may benefit for up to 8 months by adding amantadine 200-400 mg/day for the treatment of dyskinesias. • Reducing the dose size of levodopa has been beneficial in reducing

Clinical Guideline	Recommendation(s)
	dyskinesias. The risk of off-time increases but can be compensated by increasing the frequency of levodopa dosing. • Discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors can help control dyskinesias, however the risk of worsening off-time increases. • The addition of clozapine or quetiapine has shown to be beneficial in reducing peak dose dyskinesia. Clozapine's adverse effect of agranulocytosis limits its use. • Deep brain stimulation of the subthalamic nucleus allows the reduction of dopaminergic treatment. • Apomorphine given as a continuous subcutaneous infusion under direct medical supervision allows for the reduction of levodopa therapy and helps control dyskinesias.
American Academy of Sleep Medicine (AASM): **Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder (2004)**[28]	• The dopamine agonist's pramipexole and ropinirole are effective in the treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). • Levodopa with decarboxylase inhibitor and pergolide are effective in the treatment of RLS and PLMD. • Other dopamine agonists (talipexole, cabergoline, piribedil and alpha-dihydroergocryptine) may be effective in the treatment of RLS or PLMD, but the degree of efficacy of these agents has not been established. • The dopaminergic agents amantadine and selegiline may be effective in the treatment of RLS and PLMD, but the degree of efficacy of these agents has not been established. • No specific recommendations can be made regarding dopaminergic treatment of RLS or PLMD in the pediatric population or in pregnant women.
AASM: **Practice Parameters for the Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder (1999)**[29]	• Pramipexole and ropinirole were not included in this guideline as these agents were not available at the time of publication.
European Federation of Neurological Societies Task Force (EFNS): **Guidelines on Management of Restless Legs Syndrome and Periodic Limb Movement disorder in Sleep (2006)**[30]	<u>Primary RLS</u> • Ropinirole is effective in improving RLS scale scores, quality of life, sleep latency and the Periodic Leg Movements in sleep Index/Arousals (PLMS-I/PLMS-A) at an average dose of 1.5 to 4.6 mg per day. • Pramipexole, bromocriptine, oxycodone, carbamazepine and valproate are probably effective in primary RLS. • Cabergoline raises RLS scores at doses of 0.5 to 2 mg once daily and is possibly effective long term. • Pergolide improves RLS severity and subjective quality of sleep at average doses of 0.40 to 0.55 mg daily. It is possibly effective long term. • Gabapentin has demonstrated a decrease in RLS scores and improves sleep efficiency and PLMS-I at doses of 800 to 1,800 mg daily. • Levodopa/benserazide is effective in improving RLS symptoms, quality of sleep, sleep latency, PLMS-I and quality of life at an average dose of 159/40 mg at bedtime. Levodopa is possibly effective long term. • Short-term use of rotigotine 4.5 mg transdermal patch improves RLS symptoms.

Clinical Guideline	Recommendation(s)
	• Clonazepam 1 mg at bedtime is probably effective in primary RLS however it is considered probably ineffective when dosed four times daily. • The short-term use of clonidine is probably effective in decreasing symptoms of RLS and sleep latency. • The use of oral iron supplementation and vibration are probably ineffective in the treatment of RLS. • There is insufficient evidence to make a recommendation for the use of iron dextran, magnesium oxide, amantadine, lamotrigine or topiramate. • No specific recommendations can be made in the treatment of RLS in the pediatric population or in pregnant women. <u>Secondary RLS</u> • Ropinirole and levodopa are probably effective in the treatment of RLS secondary to uremia, while iron dextran is probably effective short term for this condition. • Gabapentin is recommended as probably effective in hemodialysis related RLS. • Short-term pergolide use at a dose of 0.25 mg daily is considered probably ineffective in the treatment of RLS secondary to hemodialysis. • There is insufficient evidence to support the use of benzodiazepines, opioids, clonidine, phenoxybenzamine, propranolol and talipexole in secondary RLS. <u>PLMD</u> • There is not enough evidence available to determine the effectiveness of non-ergot derivatives or antiseizure medications in PLMD. • Bromocriptine is probably effective in PLMD secondary to narcolepsy. • Clonazepam 0.5 to 2.0 mg per day and levodopa are probably effective in reducing PLMS-I and PLMS-A. • Triazolam 0.125 to 0.500 mg/day is probably effective in improving sleep efficiency but not in the reduction of PLMS. • Modafinil and propoxyphene are probably ineffective while transdermal estradiol is considered ineffective for the treatment of PLMD. • No specific recommendations can be made in the treatment of PLMD in the pediatric population or in pregnant women.
Medical Advisory Board of the Restless Legs Syndrome Foundation **An Algorithm for the Management of Restless Legs Syndrome (2004)**[31]	<u>Daily RLS</u> • Dopamine agonists are the drugs of choice in most people with daily RLS. Pramipexole and ropinirole are associated with fewer side effects; therefore they are preferred over pergolide. • Gabapentin is considered an alternative to dopamine agonists especially in patients with neuropathic pain. • Low-potency opioids such as propoxyphene or codeine and opioid agonists like tramadol are recommended as alternative treatment. • Nonpharmacological management, such as the discontinuation of medications that may exacerbate RLS (neuroleptic agents, metoclopramide, sedating antihistamines), is recommended in both daily and intermittent RLS. Bupropion may be considered in patients whose symptoms are worsened by antidepressants. • Avoiding caffeine, nicotine, and alcohol, the implementation of mental alerting activities and iron replacement in patients with iron deficiency should also be considered.

Clinical Guideline	Recommendation(s)
	Intermittent RLS • Dopamine agonists such as pramipexole or ropinirole administered intermittently may be effective but are not useful once symptoms have already begun. • The occasional use of immediate-release carbidopa/levodopa may be helpful for RLS symptoms that arise in the evening, at bedtime, during sleep or with certain activities, whereas the controlled-release formulation can be administered prior to bedtime for night-time awakenings. Levodopa has been associated with augmentation and rebound of symptoms. • Intermittent administration of low-potency opioids such as propoxyphene or codeine and opioid agonists like tramadol before sleep can successfully treat occasional RLS symptoms. • Benzodiazepines or benzodiazepine agonists may be effective when given prior to bedtime especially in patients with concurrent insomnia. Refractory RLS • Patients may respond differently to each dopamine agonist therefore switching agents is recommended if one is ineffective. • Changing to gabapentin is recommended in patients not adequately responding to initial therapy. • The addition of a second agent such as gabapentin, a benzodiazepine or an opioid is recommended in patients refractory to first-line therapy. • Switching to a high-potency opioid may be considered. This class of medication may be highly effective in the management of RLS symptoms.

Conclusions

Pramipexole and ropinirole are nonergot-derivative dopamine agonists Food and Drug Administration (FDA) approved for both the management of the signs and symptoms of idiopathic Parkinson's disease and moderate-to-severe primary Restless Legs Syndrome (RLS).

The efficacy of these agents in the treatment of Parkinson's disease is well established, although they do not appear to be as effective as levodopa in improving the motor impairments that are characteristic of the condition. Dopamine agonists are less often associated with the abnormal involuntary movements and wearing off phenomenon that limit long-term levodopa therapy. Therefore, these agents may be considered for initial therapy, especially in younger patients, to delay the use of levodopa and the development of the motor complications associated with the drug.[26] Pramipexole and ropinirole may also be used in combination with levodopa to allow for a decrease in levodopa dose.[14-17]

Pramipexole and ropinirole are the only medications FDA-approved for the treatment of RLS. They are considered effective in primary RLS and the drug of choice in most patients with daily RLS.[31] The major route of elimination of pramipexole is renal excretion and dosing must be adjusted in patients with renal impairment, whereas ropinirole is extensively metabolized by the liver and may interact with drugs that undergo CYP1A2 metabolism.[4-6] The side effect profiles for these agents are comparable, although pramipexole has shown a higher rate of hallucinations and ropinirole an increased risk of developing somnolence and hypotension.[10] Finally, ropinirole is available both as an extended-release product and generically as an immediate-release tablet.

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Generic ropinirole, bromocriptine and Mirapex® are preferred on The Office of Vermont Health Access (OVHA) preferred drug list. Parlodel®,and Requip® require prior authorization with the following approval criteria:

Parlodel®, Requip®

- The patient has had a documented intolerance to the generic product.

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